IN THE CLAIMS

Please cancel claims 16-25 without prejudice to resubmission. Please amend claims 1 and 2 to read as follows:

1. (Twice Amended) A composition for the treatment of diabetic neuropathy by a method of administration selected from the group consisting of oral administration, parenteral administration and inhalation, the composition comprising a mixture of an amount of a compound that promotes synthesis of nerve growth factor selected from the group consisting of vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, pharmaceutically acceptable salts thereof and mixtures thereof, which is effective when administered in the composition to promote synthesis of nerve growth factor, an amount of an aldose reductase inhibitor which is effective when administered in the composition to inhibit aldose reductase and an effective amount of an antioxidant.

2. (Twice Amended) A composition as claimed in claim 1, wherein the compound that promotes the synthesis of nerve growth factor is selected from the group consisting of: vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, and mixtures thereof.

REMARKS

This Amendment is responsive to the Office Action dated July 18, 2001. Claims 1 and 2 have been amended. Claims 16-25 have been canceled without prejudice to resubmission. Claims 1-15 are currently pending in the present application.

Restriction Requirement

In response to the Final Restriction Requirement, applicant has canceled claims 16-25 drawn to the non-elected invention, which was not elected in Paper No. 4, with traverse. It is considered that the cancellation of claims 16-25 satisfies the requirement of 37 C.F.R. §1.144 with respect to the restriction requirement.

35 U.S.C. §112 Objection

The specification was objected to under 35 U.S.C. §112, first paragraph, as failing to adequately teach how to make and/or use the invention on the specific basis that the specification does not reasonably provide enablement for, "...other vitamin D_3 derivatives which promote the synthesis of nerve growth factor." Although the applicant does not concede that this objection is correct, the applicant has amended the claims to delete the phrase "...other vitamin D_3 derivatives which promote the synthesis of nerve growth factor" from all pending claims in order to obviate this objection. Favorable consideration and withdrawal of the objection in view of the amendments is respectfully requested.

35 U.S.C. §112 Rejections

Claims 1, 2 and 6 have been rejected pursuant to 35 U.S.C. §112, first paragraph, on the basis that the specification is not enabling a person skilled in art use "...other vitamin D_3 derivatives which promote the synthesis of nerve growth factor." Although the applicant does not concede that this rejection is correct, the applicant has amended the claims to delete the phrase "...other vitamin D_3 derivatives which promote the synthesis of nerve growth factor" from all pending claims in order to obviate this rejection. Favorable consideration and withdrawal of the rejection in view of the amendments is respectfully requested.

Claim 2 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite on the basis that there is insufficient antecedent basis in claim 1 for the limitation "topical composition as claimed in claim 1" which appears in line 1 of claim 2. Claim 2 has been amended to delete the word "topical" from line 1 in order to obviate this rejection. Favorable consideration and withdrawal of the rejection in view of this amendment to claim 2 is respectfully requested.

Claims 1-6, 10, 12-13 and 15 have been rejected pursuant to 35 U.S.C. §112, second paragraph, on the basis that "vitamin D_3" or "a vitamin D_3" recites a narrower range within a broader range "...other vitamin D3 derivatives which promote the synthesis of nerve growth factor." Although the applicant does not concede that this rejection is correct, the applicant has amended the claims to delete the phrase "...other vitamin D_3 derivatives which promote the synthesis of nerve growth factor" from all pending claims in order to obviate this rejection.

Favorable consideration and withdrawal of the rejection in view of the amendments is respectfully requested.

35 U.S.C. § 103(a) Rejection

Claims 1-6, 10, 12-13, and 15 have been rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,976,568 (hereinafter "Riley"). This rejection is respectfully traversed and reconsideration is requested for the reasons, which follow.

Amended claim 1 of the present application requires composition comprising a mixture of an amount of a compound that promotes synthesis of nerve growth factor selected from the group consisting of vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, pharmaceutically acceptable salts thereof and mixtures thereof, which is effective when administered in the composition to promote synthesis of nerve growth factor, an amount of an aldose reductase inhibitor which is effective when administered in the composition to inhibit aldose reductase and an effective amount of an antioxidant.

The elected species currently under examination is a composition comprising a mixture of an amount of a compound that promotes synthesis of nerve growth factor selected from the group consisting of vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, pharmaceutically acceptable salts thereof and mixtures thereof, which is effective when administered in the composition to promote synthesis of nerve growth factor, an amount of quercetin which is effective when administered in the composition to inhibit aldose reductase and an effective amount of ascorbyl palmitate to act as an antioxidant.

The Examiner first takes the position that Riley discloses an oral daily supplement composition comprising Vitamins A, D, E, C (buffered calcium ascorbate, ascorbic acid and ascorbyl palmitate) and quercetin in claim 2. However, as is clear from the specification, and in particular Example 2 of Riley, the table of claim 2 and Example 2 relates to a total daily dosage range which may be taken by an individual in the form of several distinct modular formulations. Thus, claim 2 does not disclose a particular composition but rather discloses a total daily dosage range, which is achieved via intake of several distinct modular formulations, each of which has a

different composition (see e.g. column 20, lines 42+, Tables II-III, which described the distinct modular formulations, and claims 3-5 which also describe the distinct modular formulations).

Moreover, the total daily dosage range of claim 2 differs from the elected species of the present application in at least the following respects:

1. It does not mention vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, pharmaceutically acceptable salts thereof and mixtures thereof;
2. quercetin is an optional ingredient of claim 2 since it may be present in an amount of 0.0 to 500 mg;
3. claim 2 does not mention that ascorbyl palmitate is included in the daily dosage; and
4. claim 2 does not specify an amount of ascorbyl palmitate in the daily dosage.

Accordingly, the skilled person starting from the oral daily dosage of claim 2 of Riley must take the following steps to arrive at the elected species of the present invention:

1. Select the particular form of vitamin D claimed in the claims of the present application;
2. select an amount of the particular form of vitamin D which is effective to promote synthesis of nerve growth factor;
3. decide to include quercetin as an ingredient in the composition;
4. select an amount of quercetin which is effective to act as an aldose reductase inhibitor;
5. select ascorbyl palmitate as an appropriate form of vitamin C for inclusion in the composition; and
6. select an amount of ascorbyl palmitate that is effective to act as an antioxidant.

For each of these six steps, the Examiner must provide some teaching or motivation in Riley to make the necessary selection of ingredients. Riley does not provide the required teaching or motivation for any of the foregoing six steps, and certainly not to carry out all six steps required to arrive at the present invention.

Specifically, based on the disclosure of claim 2 of Riley, the skilled person has no reason to pick the specific form of vitamin D claimed in the present claims. Rather, claim 2 only gives a generic disclosure of vitamin D and there are many forms of vitamin D, which are not included

in the present claims. Thus, the skilled person has no motivation to selected, for example, vitamin D_3 as the Examiner suggests.

The Examiner apparently relies on the Examples of Riley to provide a motivation to select vitamin D_3 as the appropriate form of vitamin D to employ in the composition of claim 2. However, it is important to note that Riley clearly avoids a combination of quercetin with vitamin D_3 in all of its examples. More specifically, in both versions of Modules 2, 5 and 6, and all four versions of Module I shown in Tables II-III of Riley, vitamin D_3 is employed and quercetin is always left out of the composition. Then, in all four versions of Module 3 and both versions of Module 7, quercetin is employed but vitamin D_3 is left out. In fact, sixteen compositions disclosed in Riley have one of vitamin D_3 or quercetin but none of the sixteen compositions include both of these compounds together in the same composition. From these numerous examples, the skilled person would clearly be led not to put quercetin and vitamin D_3 in the same composition.

The Examiner has also failed provide any evidence that the skilled person using the teachings of Riley would select an amount of vitamin D_3 effective to promote the synthesis of nerve growth factor or an amount of quercetin effective to act as an aldose reductase inhibitor. Riley does not mention either the desirability of using vitamin D_3 to promote the synthesis of nerve growth factor or the desirability of using quercetin as an aldose reductase inhibitor. Thus, the skilled person has no basis in the teachings of Riley to arrive at these respective effective amounts since the functions of these materials in the claimed composition is not even disclosed in Riley.

Further, the Examiner apparently basis his conclusion that the vitamin C of claim 2 of Riley is "buffered calcium ascorbate, ascorbic acid and ascorbyl palmitate" on the Examples in Tables II-III of Riley. However, Riley nowhere discloses the quantity of ascorbyl palmitate which is employed nor does claim 2 of Riley indicate anywhere that the vitamin C should include ascorbyl palmitate. Thus, the skilled person when starting with Example 2 of Riley, must first decide to use ascorbyl palmitate and then use a sufficient amount of ascorbyl palmitate to provide an antioxidant effect, in order to arrive at the present invention. Since Riley nowhere discloses the amount of ascorbyl palmitate employed, there is no basis whatsoever in Riley for reaching the conclusion that it would be obvious to employ the amount of ascorbyl palmitate required by the claims of the present application.

Finally, none of the examples of Riley teaches or suggests a combination of quercetin, ascorbyl palmitate and vitamin D_3 and, in fact, the Examples specifically leave out one of quercetin or vitamin D_3 from each of the sixteen Modules disclosed in Tables II-III of Riley.

For these reasons, it is considered that the elected species is clearly patentable over claim 2 of Riley.

The Examiner also relies on the compositions of claim 3 and Table II of Riley in support of this rejection. First, the two separate oral dosage compositions of claim 3 of Riley are the same as the AM and PM Modules 1 of Table II of Riley. In order to arrive at the present invention starting from these compositions of Riley, the skilled person would have to make the following modifications:

1. select an amount of vitamin D_3 which is effective to promote synthesis of nerve growth factor;
2. decide to include quercetin as an ingredient in the composition (claim 3 of Riley does not mention quercetin and the compositions of Table II of Riley never include quercetin in the same composition as vitamin D_3);
3. select an amount of quercetin which is effective to act as an aldose reductase inhibitor;
4. select ascorbyl palmitate as an appropriate form of vitamin C for inclusion in the composition (claim 3 of Riley does not mention ascorbyl palmitate); and
5. select an amount of ascorbyl palmitate that is effective to act as an antioxidant.

The Examiner has provided no teaching or suggestion in Riley to make any one of the five modifications listed above nor has the Examiner provided any evidence that the amount of vitamin D_3 employed in claim 3 of Riley is an amount effective to promote the synthesis of nerve growth factor. Accordingly, the rejection of all claims of the present application, at least insofar as they are directed to the elected species, should be withdrawn on this basis.

Finally, with respect to the subject matter of claims 1-15, taken as a whole, these claims are clearly unobvious over Riley since Riley does not teach or suggest any composition which includes both vitamin D_3 and quercetin and Riley does not contain and teaching, suggestion or motivation to combine these two ingredients in a single composition. In fact, Riley teaches away from this combination by providing sixteen Modules, which employ only one of vitamin D_3 or quercetin but never both in the same composition. This would certainly lead a skilled person not

to combine quercetin and vitamin D_3 in the same composition. Finally, the Examiner has not pointed out any other antioxidants in the composition of Riley. Therefore, for at least these reasons, the entire subject matter of claims 1-15 is considered to unobvious over Riley.

Favorable consideration and issuance of a Notice of Allowance is respectfully requested.

Respectfully submitted,

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MARKED UP COPY OF THE AMENDED CLAIMS

1. (Twice Amended) A composition for the treatment of diabetic neuropathy by a method of administration selected from the group consisting of oral administration, parenteral administration and inhalation, the composition comprising a mixture of an amount of a compound that promotes synthesis of nerve growth factor selected from the group consisting of vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, pharmaceutically acceptable salts thereof and mixtures thereof, which is effective when administered in the composition to promote synthesis of nerve growth factor, an amount of an aldose reductase inhibitor which is effective when administered in the composition to inhibit aldose reductase and an effective amount of an antioxidant.

2. (Twice Amended) A ~~topical~~ composition as claimed in claim 1, wherein the compound that promotes the synthesis of nerve growth factor is selected from the group consisting of: vitamin D_3~~; a vitamin D_3 derivative~~, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, ~~and other vitamin D_3 derivatives which promote the synthesis of nerve growth factor, pharmaceutically acceptable salts thereof~~ and mixtures thereof.